

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS**

ABBOTT GMBH & CO., KG, ABBOTT
BIORESEARCH CENTER, INC., ABBOTT
BIOTECHNOLOGY, LTD.

Plaintiffs,

v.

CENTOCOR ORTHO BIOTECH, INC.,
CENTOCOR BIOLOGICS, LLC.

Defendant.

C.A. No. 4:09-CV-11340 (FDS)

JURY TRIAL DEMANDED

ABBOTT'S SUPPLEMENTAL CLAIM CONSTRUCTION BRIEF
REGARDING THE TERM "HUMAN ANTIBODY"

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I. ABBOTT’S PROPOSED CONSTRUCTION OF THE TERM “HUMAN ANTIBODY” SHOULD BE ADOPTED OVER CENTOCOR’S PROPOSED CONSTRUCTION

Abbott respectfully submits this supplemental brief in support of its position that the term “human antibody” should be construed to mean “an antibody that is derived from human DNA and not from the DNA of any non-human species.” The language of the patents-in-suit, the understanding of the term from the perspective of someone of ordinary skill in the art at the relevant time, and both of the parties’ prior statements and positions regarding the term “human antibody” support this construction over Centocor’s proposed construction, which is based on specification language that is exemplary, and not definitional.¹

“human antibody”	
ABBOTT’S PROPOSED CONSTRUCTION	CENTOCOR’S PROPOSED CONSTRUCTION
“An antibody that is derived from human DNA and not from the DNA of any non-human species.”	“A human antibody includes antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by Kabat et al. (See Kabat, et al. (1991) Sequences of proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242), but the antibody can have up to twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence.”

A. Centocor’s Exclusionary Construction is Inconsistent With The Relevant Exemplary Specification Language

The relevant common specification language that follows the term “human antibody” in the patents-in-suit, and on which Centocor relies for its proposed claim construction, states that

¹ Abbott also respectfully requests that the Court consider the arguments set forth at pages 8-17 of Abbott’s Opp. to Centocor’s Mot. to Amend Claim Construction Pleadings (“Abbott’s Opp. Mem.”), dated March 7, 2011. A redacted version of this brief was filed as Docket Entry No. 132, with a supporting declaration and accompanying non-confidential exhibits filed as Docket Entry No. 131. A complete version of this brief, along with supporting Exhibits 3, 4, 5, 6, 10, 11, and 18 were sealed with the Court on March 9, 2011, at Docket Entry No. 134. Courtesy copies of the full versions of Abbott’s Opp. Mem. and supporting documents were sent to the Court on March 9.

“[t]he term ‘human antibody’ *includes* antibodies having variable and constant regions corresponding to human germline immunoglobulin sequences as described by” the 1991 version of the Kabat printed (non-electronic) listing of germline sequences that had been discovered as of 1991. (Pearson Feb. 22 Decl.² Ex. 5, U.S. Patent 6,914,128 (“‘128 Patent”) at col.26 l.55-col.27 l.60 (emphasis added); *see also* Gunther Mar. 7 Decl.³ Ex. 12, Johnson and Wu, *Kabat Database and Its Applications: 30 Years After the First Variability Plot*, 28 NUCLEIC ACIDS RESEARCH, No. 1, 2000 at 214 (discussing updates to Kabat sequence listings since 1991).) It goes on to state that “[t]he human antibody *can have* up to twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence.” (‘128 Patent at col.27 l.4-col.27 l.6 (emphasis added).) Finally, it states, “[h]owever, the term ‘human antibody’, as used herein, *is not intended to include* antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.” (*Id.* at col. 27:10-14 (emphasis added).)

According to the plain language of the specification, the term “human antibody” *can* include antibodies with the exemplary characteristics described in this portion of the specification, but it is not limited to such antibodies. *See, e.g., SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1284 (Fed. Cir. 2005) (“As a patent law term of art, ‘includes’ means ‘comprising.’ . . . Neither includes, nor comprising, forecloses additional elements that need not satisfy the stated claim limitations.”). Therefore, the term can include antibodies with other characteristics, including antibodies with more than twenty positions replaced with amino

² “Pearson Feb. 22 Decl.” refers to the Declaration of Mathew A. Pearson in Support of Defendants’ Motion to Amend Claim Construction Pleadings, filed by Centocor on February 22, 2011, as Docket Entry No. 121.

³ “Gunther Mar. 7 Decl.” refers to the Declaration of Robert J. Gunther, Jr. in Support of Abbott’s Opposition to Centocor’s Motion to Amend Claim Construction Pleadings, filed on March 7, 2011, as Docket Entry No. 131, with supporting exhibits.

acid residues which are not part of the human germline sequence, or antibodies that correspond to the human germline sequences listed in other sources, besides the specific 1991 Kabat print publication. (*See also* Abbott's Opp. Mem. at 6-7, 9-11.)

Indeed, throughout the common specification, a different, electronic germline sequencing database called Vbase is used by the inventors in 1999 to compare Abbott's preferred embodiment antibodies to human germline sequences. (*See* '128 Patent at fig. 1, col.23 l.58-col.24 l.5, col.25 ll.56-59, col.41 ll.1-8, col.41 l.65-col.42 l.2, col.44 ll.44-47, col.44 l.63-col.45 l.2, appendix A, table 1, col.104 ll.33-38; *see also* Gunther Mar. 28 Decl.⁴ Ex. 20, (table of references to Vbase database in '128 Patent).) This Vbase electronic database was updated regularly to include additional germline sequences discovered after 1991, which the 1991 Kabat print listing would not have contained.⁵ *See* <http://vbase.mrc-cpe.cam.ac.uk/>. Additionally, a comparison of Vbase germline sequences to the sequences of the variable regions of the heavy chain and light chain of these exemplary Abbott antibodies reveals that many of the antibodies have *more* than twenty positions replaced with amino acid residues which are not part of the human germline immunoglobulin sequence. (*See* '128 Patent at fig. 1, col.23 l.58-col.24 l.5.) Therefore, an interpretation of the term "human antibody" in accordance with Centocor's proposed construction may improperly exclude such preferred embodiments, a result that would be incorrect under the law. *See Oatey Co. v. IPS Corp.*, 514 F.3d 1271, 1276-77 (Fed. Cir. 2008) ("We normally do not interpret claim terms in a way that excludes embodiments disclosed in the

⁴ "Gunther Mar. 28 Decl." refers to the Declaration of Robert J. Gunther, Jr. in Support of Abbott's Supplemental Claim Construction Brief Regarding the Term 'Human Antibody,' filed on March 28, 2011, contemporaneously with this brief.

⁵ Notably, Kabat germline sequences are now also published in the form of an electronic database, which has been updated with newly-discovered germline sequences since 1991. *See* <http://www.kabatdatabase.com/index.html>. Therefore, a comparison of antibodies that is limited to the sequences listed in the 1991 print edition of Kabat may not result in an accurate comparison to human germline, as it was known in 1999 and as it is known today.

specification.”) (citing *Vitronics Corp. v. Conception, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996) (additional citations omitted)). (*See also* Abbott’s Opp. Mem. at 11-12.)

B. Abbott’s Proposed Construction is Supported by the Specification and the Understanding of an Ordinary Person of Skill in the Art at the Time

It is also clear from the relevant portion of the common specification that the term “human antibody” is not meant to include antibodies with sequences “derived from the germline of another mammalian species, such as a mouse” (‘128 Patent at col.27 ll.10-13.) This is consistent with Abbott’s proposed construction of “human antibody” as an antibody that is derived from human DNA and not from the DNA of any non-human species. It is also consistent with the use of the term “human antibody” throughout the patents-in-suit, as referring to embodiment antibodies that, although are not identical in sequence, all originated from phage display libraries made from human DNA. (*See, e.g., id.* at col.4 l.7-col.9 l.27.)

This understanding of the term “human antibody” is also how a person of ordinary skill in the art at the time would interpret the term – as an antibody derived from human DNA, as opposed to the DNA of any non-human species. (*See, e.g.,* Gunther Mar. 28 Decl. Ex. 21, Neuberger et al., *Mice Perform a Human Repertoire*, NATURE, March 16, 1997, at 25, fig. 1 (describing phage display and transgenic mice technologies as “[s]trategies for making human mAbs” because these technologies use human-sourced DNA, as opposed to DNA sourced from other species).)

C. Abbott’s Proposed Construction is Consistent with the Parties’ Prior Statements and Positions

Abbott’s proposed claim construction is also consistent with Abbott’s prior statements regarding the term “human antibody,” including the statements of its expert Brent Iverson during the interference proceeding initiated by Centocor with the United States Patent and Trademark Office’s Board of Patent Appeals and Interferences (“BPAI”) in December 2007

(“Interference”). As discussed fully in Abbott’s Opposition Memorandum at 12-13, Dr. Iverson distinguished prior art references relied on by Centocor in the Interference that disclose non-human mouse and rat antibodies, from the technology described in the ‘128 Patent, which discloses human antibodies derived from human DNA. (*See* Pearson Feb. 22 Decl. Ex. 12, Iverson Decl. at ¶ 16 (“All of the IL-12 references relied on by Centocor disclose research antibody sequences from non-humans”); *see also* Gunther Mar. 7 Decl. Ex. 15, Iverson Tr. at 63:9-15 (“I believe the term ‘human antibody’ refers to an antibody that is derived from a human This is distinct from sequences derived from antibodies . . . from other species that have been grafted in.”).) Dr. Iverson’s statements only further underscore that the term “human antibody” is understood by experts in the art to mean an antibody that is derived from human DNA and not from the DNA of any non-human species. In its decision in favor of Abbott on Centocor’s obviousness motion in the Interference, the BPAI quoted Dr. Iverson’s definition of human antibody favorably, stating that “[h]uman antibodies’ means human not part human and part something else[,]” without ever adopting or relying on the exemplary human germline characteristics discussed in the specification. (Gunther Mar. 7 Decl. Ex. 16, BPAI Memorandum Opinion (Aug. 6, 2009) at 27-29.)

Notably, Abbott’s proposed construction is further consistent with what Centocor’s position on the meaning of “human antibody” has been until now. (*See* Abbott’s Opp. Mem. at 16-17.) In particular, in order to bring an interference action, Centocor specifically argued that the antibody in its accused product, Stelara, was a “human antibody” as that term is used in the ‘128 Patent. (*See* Gunther Mar. 7 Decl. Ex. 9 at 5 (Centocor’s Declaration of Interference reciting Count I of the Interference as “[a]n isolated *human antibody* according to claim 1 of U.S. Application 10/912,994 or claim 1 of U.S. Patent 6,914,128.”) (emphasis added).) Without such

an argument, Centocor would not have been able to seek an interference to assert priority of Centocor's patent application over Abbott's '128 Patent. Likewise, Centocor's product label specifically describes the accused product as a human antibody. (*See* Gunther Mar. 7 Decl. Ex. 5 at ABT-IL-12-00000008; *see also* Gunther Decl. Ex. 6, EMEA Annex I Summary of Product Characteristics of Stelara at ABT-IL-12-00000018.) Now, however, Centocor urges this Court to adopt an improperly narrow claim construction position in an effort to argue that its accused product is not a human antibody. Centocor cannot have it both ways.

Centocor's witnesses have testified that the term "human antibody" has a meaning that is much broader than the one Centocor now proposes. (*See* Abbott's Opp. Mem. at 17; Gunther Mar. 7 Decl. Ex. 17 at 12:23-13:23 (Centocor's Karyn T. O'Neil testifying that a "human antibody" is any antibody that has "over 80 percent" "sequence identity" with "or sequence homology" to a human gene or human germline sequences, a much broader definition than the "up to twenty positions replaced with amino acid residues" Centocor now proposes⁶); Gunther Mar. 7 Decl. Ex. 19 at 37:7-10 (Centocor's Kimberly Staquet testifying that a "human antibody . . . is fully human, does not contain any portions from other species"); Centocor's Rebuttal to Abbott's Opp. Mem. (filed as Ex. 1 to Centocor's Request for Leave to File a Rebuttal (Mar. 10, 2011), Dkt. No. 135) at 5-6 (Centocor's John Ghrayeb testifying that "[h]uman is something that comes from you and me"); *id.* at 6 (Centocor's Jill Giles-Komar stating that a human antibody "comes from human DNA").) This further underscores the inconsistency and unreasonableness of Centocor's position, and the validity of Abbott's proposed construction.

⁶ Centocor's position that a human antibody has over 80% sequence identity to a human germline allows for there to be about 20% of the sequence changed from human germline. Centocor's accused product, Stelara, has 1,326 amino acids. Twenty percent of 1,326 is about 265. In this case, therefore, Stelara could have about 265 amino acid changes and still be considered a human antibody. This definition is much broader than the purported limit of 20 amino acid changes that Centocor is now proposing.

II. CONCLUSION

For the reasons set forth herein and in Abbott's Opposition Memorandum, Abbott respectfully requests that the Court construe the term "human antibody" to mean "an antibody that is derived from human DNA and not from the DNA of any non-human species."

Respectfully submitted,

Dated: March 28, 2011

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CERTIFICATE OF SERVICE

I certify that, on March 28, 2011, this document (filed through the ECF system) will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF).

/s/Robert J. Gunther, Jr.